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厦门大学

博 士 学 位 论 文

抗多药耐药活性天然产物 Hapalosin 的不对称全合成、结构修饰和类似物库的构建以及 Melleumin A、B 的不对称全合成研究

Total Synthesis of Hapalosin and Its Analogues: Construction of Three Small Hapalosin *C*-9 Analogues Libraries and Studies on Total Synthesis of Melleumins A and B

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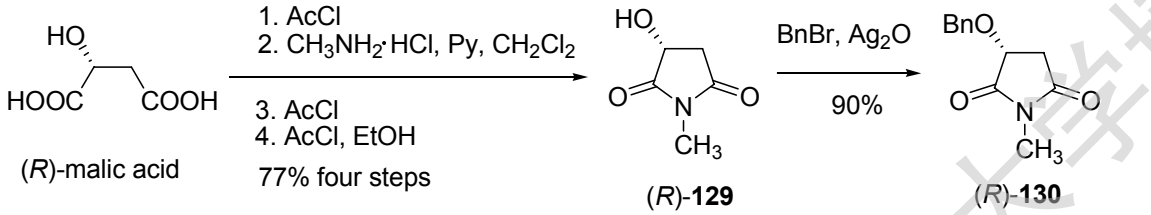
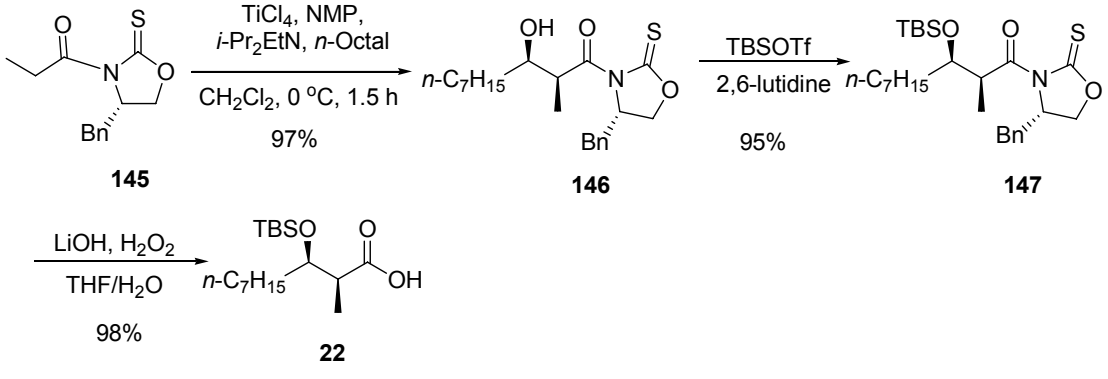
摘 要

环肽类化合物是一类结构复杂多样的天然产物。自然界中存在大量的环肽类化合物，表现出多种生物活性，如杀虫、抗菌、抗肿瘤、抗病毒、和免疫抑制等。环肽类化合物作为富有实用前景的先导化合物在药物发现中受到越来越多的关注，新的活性天然产物也不断被发现。同时，环肽类天然产物的全合成也成为不对称合成的新热点。Hapalosin（**1a**）是 1994 年从蓝藻中分离提取的一类新型结构的环肽化合物，因其对肿瘤细胞的多药耐药性细胞系有很强的抑制作用，一经发现就引起了广大合成化学家和药物化学家的关注。本论文的目标在于拓展手性合成砌块(*R*/*S*)苹果酰亚胺的多用性，将其应用于环肽类天然产物 hapalosin 和 melleumin 的全合成当中。通过本论文工作取得了以下成果：

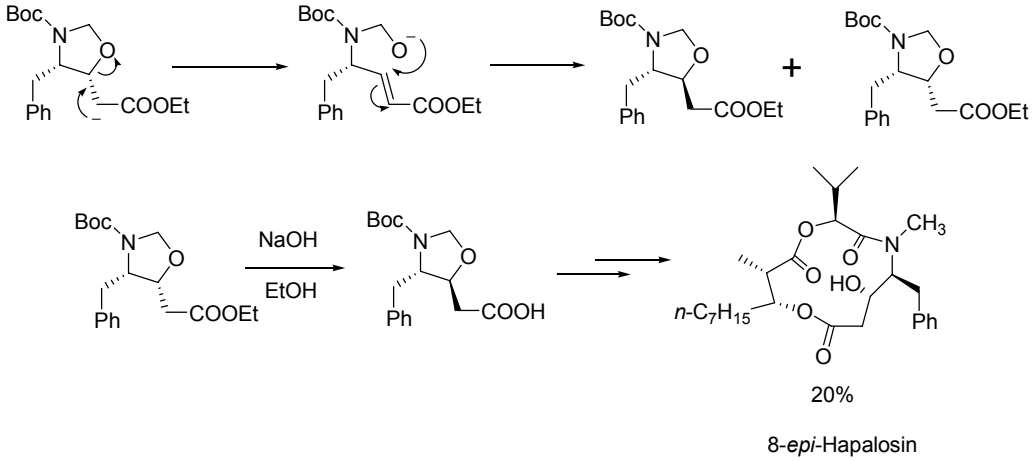
一、改进了 *N*-甲基苹果酰亚胺的合成方法，从(*R*)-苹果酸出发，采用甲氨盐酸盐替代原方法中的氨气，直接在酰亚氨的氮原子上引入甲基进而合成砌块(*R*)-**130**。在减少合成步骤的同时还避免了使用氨气在实验操作上带来的麻烦，五步总产率为 69%。



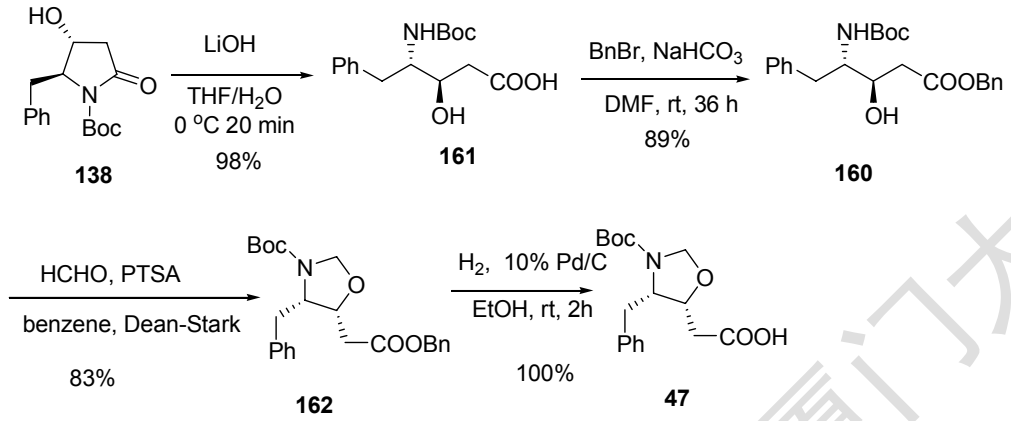
二、 完成了 hapalosin 片断 B 的改进合成，采用文献最新改进方法，用四氯化钛替代关键步骤 Evans aldol 反应所需的有机硼试剂。在保留原有路线所有优点的同时避免了有机硼试剂的价格昂贵，后处理繁琐等缺点。



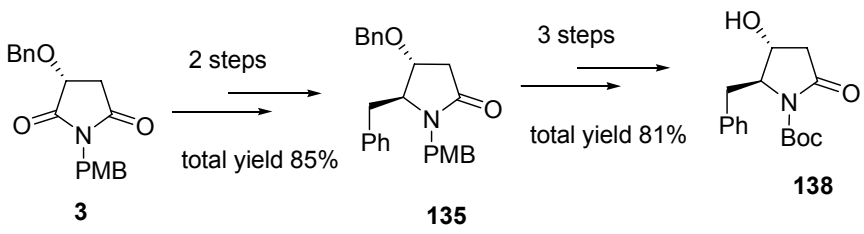
三、在合成 hapalosin 片断 C 时发现了噁唑烷乙酸酯在碱性条件下的差向异构化行为，并做了进一步研究，提出其可能经历了一个逆迈克尔加成－迈克尔加成的历程，并利用所得的差向异构化产物合成了 hapalosin 的差向异构体 8-*epi*-hapalosin。

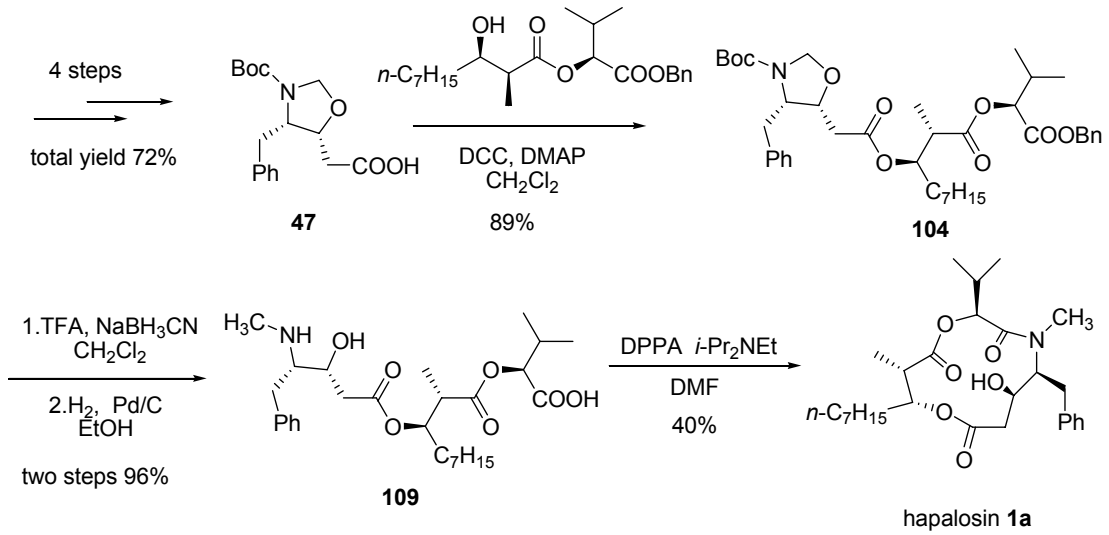


四、采用苄基替代噁唑烷乙酸酯中的乙基，用催化氢解的方法脱去苄基，由此避免了碱性条件水解引起的差向异构化，从而建立了 hapalosin 中 β-羟基-γ-氨基酸片断无差向异构化的合成方法。

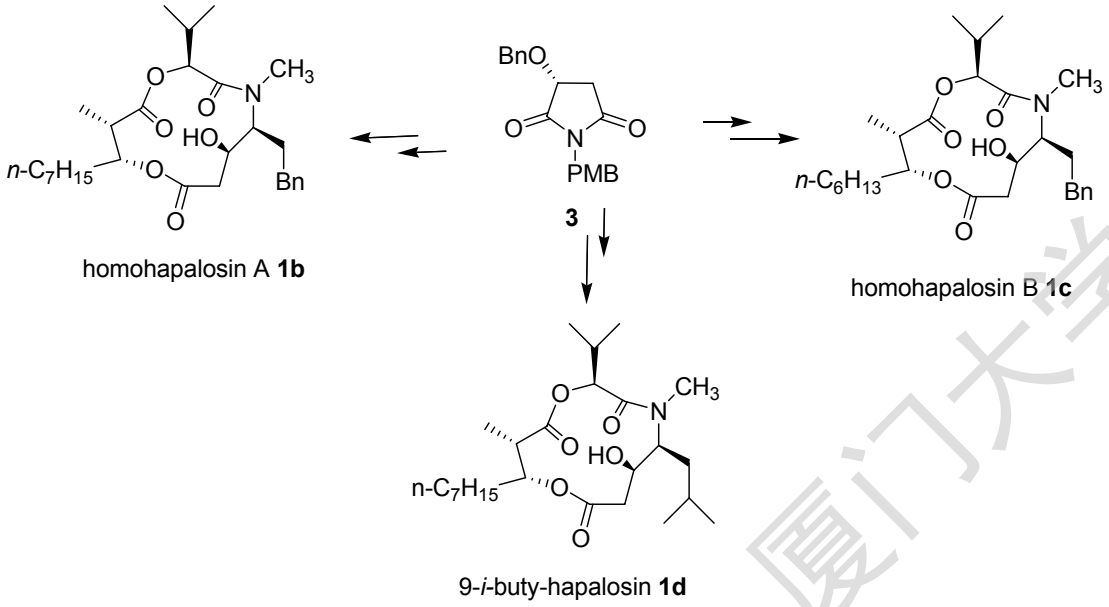


五、最终从(*R*)-苹果酰亚胺 **3** 出发经 13 步反应，以 16.9%的总产率完成了 hapalosin 的不对称全合成。由此发展了一条新的多样性导向的 hapalosin 全合成路线。

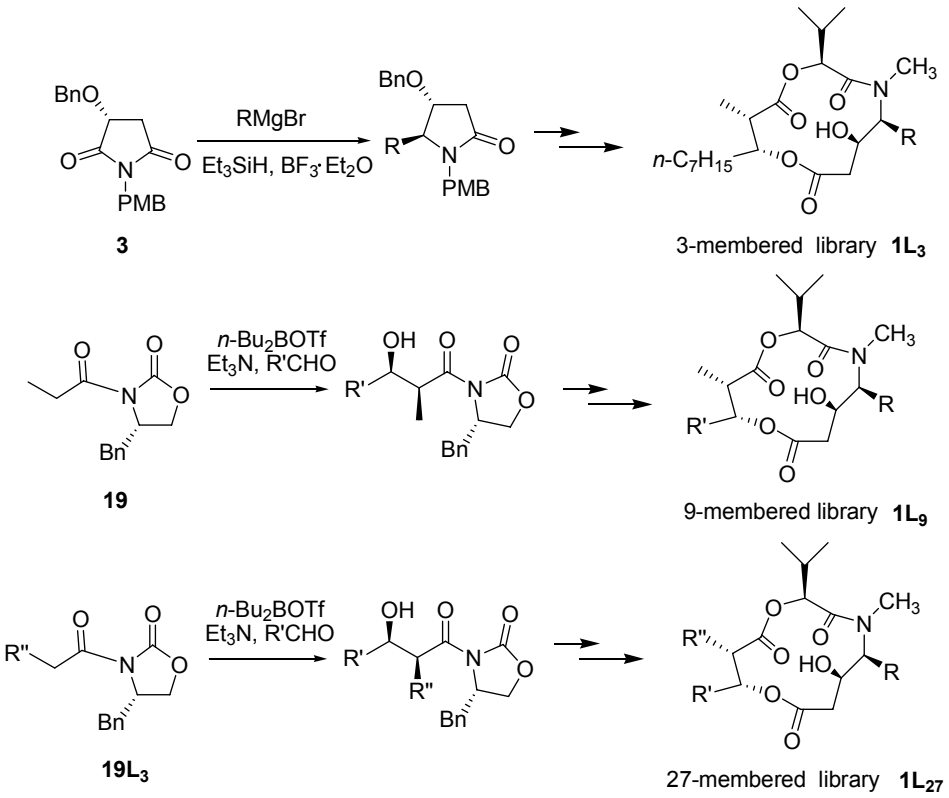




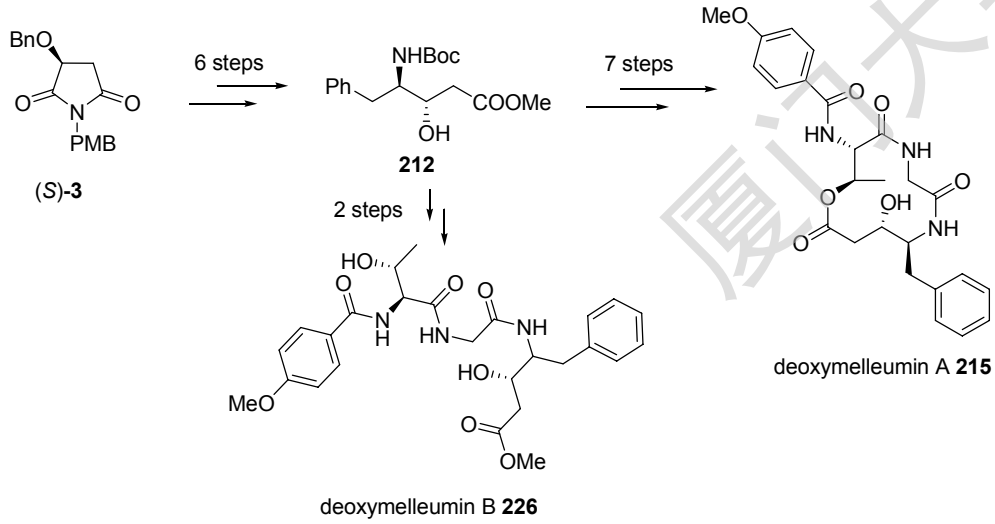
六、应用本文第二章发展的灵活多变的全合成路线，通过不同格氏试剂对合成砌块 **3** 的加成，在吡咯烷酮的 *C*-5 位引入不同的取代基，进而合成了三个 hapalosin *C*-9 改变的类似物 homohapalosin A, homohapalosin B 和 9-*i*-butylhapaolsin。为进一步研究构效关系奠定了物质基础。



七、将液相组合化学的方法引入到格氏试剂与苹果酰亚胺的加成还原烷基化当中，并将其应用于本文第二章讨论的多样性导向的 hapalosin 全合成路线当中，由此经 13 步反应建立了三组分 hapalosin 类似物库。其次将液相组合化学方法应用于 Evans aldol 反应中，由此经 9 步反应分别合成了九组分和二十七组分的 hapalosin 类似物库。结果显示各步反应均有较高的产率和较好的均一性。



八、从合成砌块(*S*)-**3** 出发经 6 步反应合成了非天然氨基酸化合物 **212**，再分别经过 7 步和 2 步反应合成了天然产物的脱氧类似物 deoxymelleumin A 和 deoxymelleumin B。应用该方法只需将苄基格氏试剂替换成对甲氧基苄基格氏试剂即可完成天然产物 melleumin A 和 melleumin B 的全合成为该两个天然产物的全合成奠定了坚实的基础。

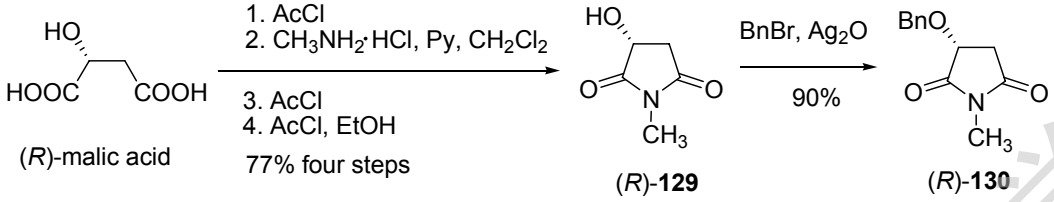


关键词： 环肽 天然产物 不对称全合成 多药耐药 组合化学 类似物 hapalosin melleumin

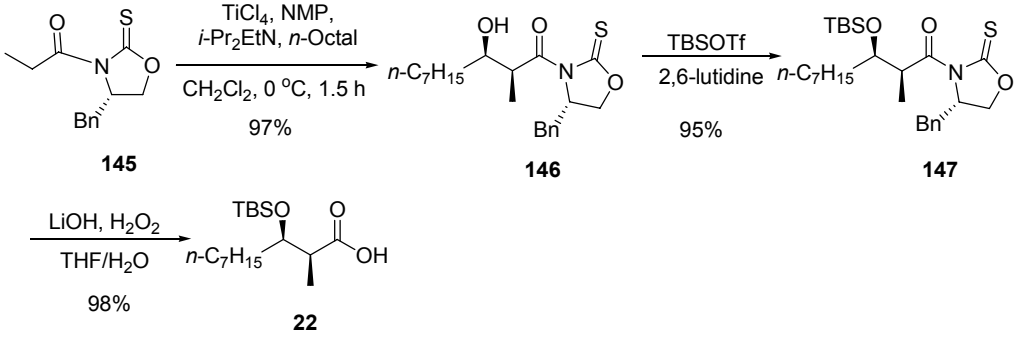
ABSTRACT

Cylcopeptides with complex and diversified structures are widespread in nature. Many of them exhibit various biological activities, such as, antibiotics, antitumor, antivirus, immunosuppressive effect and pesticides. As promising lead compounds in drug discovery, cylcopeptides are receiving more and more attention. And the studies on the asymmetric total synthesis of these compounds have been a new focus. In this dissertation, the application of malimides-based asymmetric synthesis methodology was expanded and the total syntheses of some cylcopeptides, which includes hapalosin, three analogues and three small libraries, as well as deoxy-analogues of melleumins A,B were achieved via these useful chiral building blocks. The main results and observations made from these studies are listed as follows:

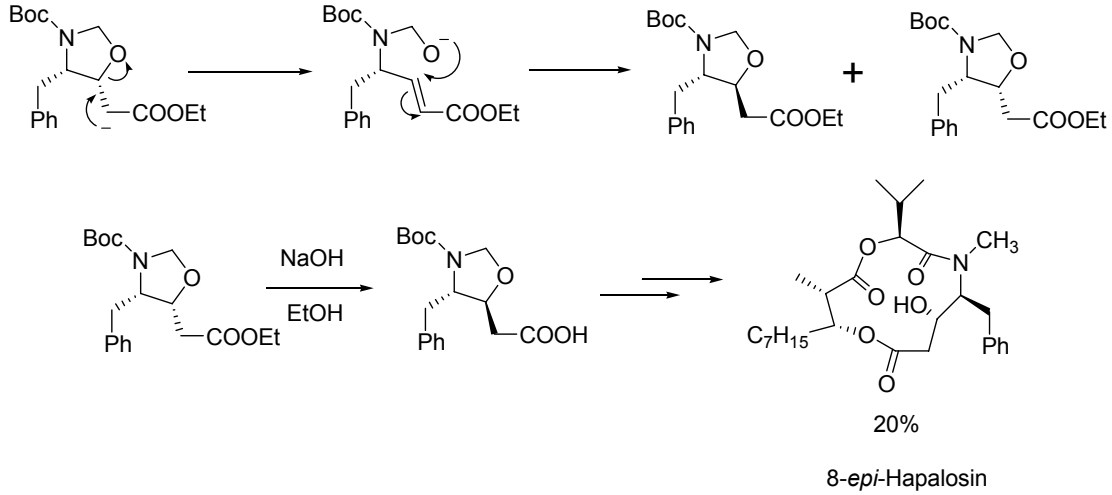
1. An improved method for the synthsis of *N*-methyl-malimide had been developed. By using the methylammonia hydrochloride to replace ammonia, the *N*-methyl malimide could be synthesized directly. The building block (*R*)-**130** was synthesized by this method in 69% yield.



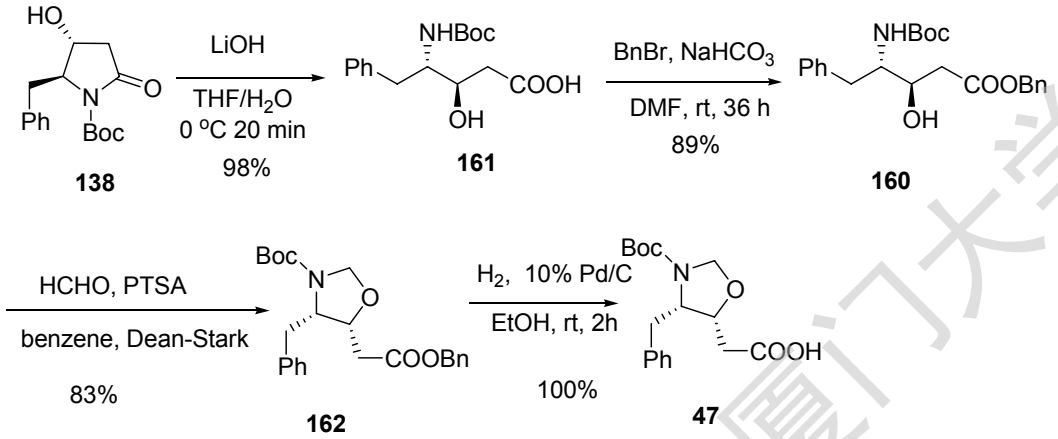
2. Recent reported improved reaction condition for the Evans aldol reaction, a key step in the synthesis of fragment B of hapalosin, was used which allows replacing the organic boron reagent with titanium tetrachloride. While all the advantages of the original route were kept down, some of the shortcomings of the original method, such as using expensive organic boron reagent and troublesome work-up, have been overcome.



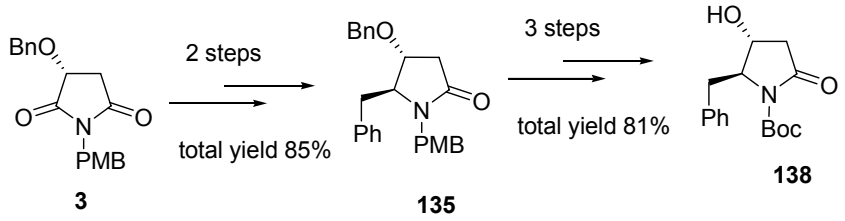
3. Epimerization of oxazolidine acetate was observed during the synthesis of the fragment C of hapalosin. A plausible mechanism for the epimerization is a retro-Michael addition-intramolecular Michael addition under basic conditions. The synthesis of an epimer of hapalosin (8-*epi*-hapalosin) was accomplished by taking advantage of this epimerization.

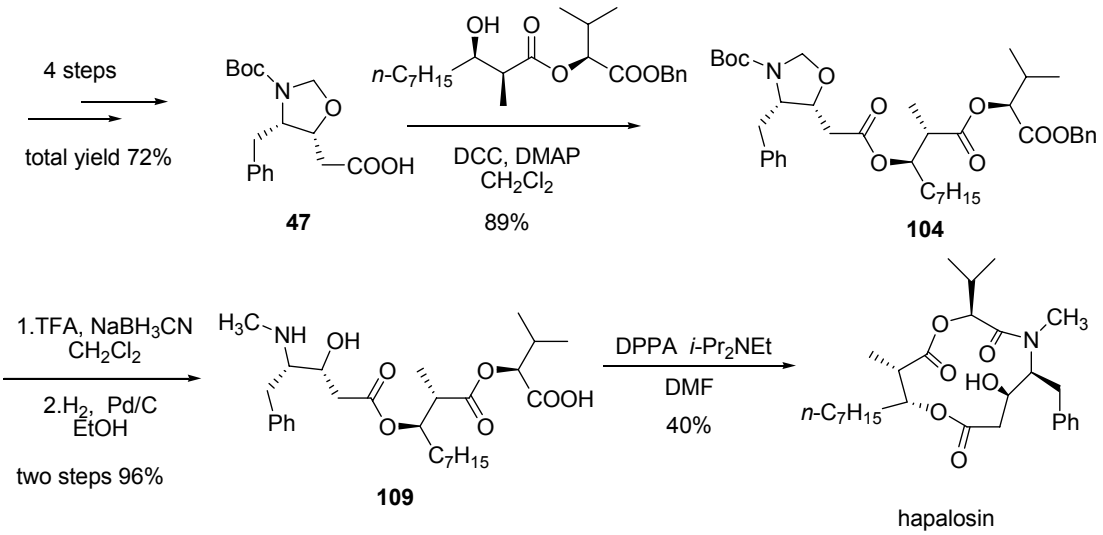


4. An epimerization-free synthesis of the γ-amino-β-hydroxy-acid moiety of hapalosin was developed by preparing the corresponding benzyl ester of oxazolidine acetate, which can be deprotected by hydrogenolysis.

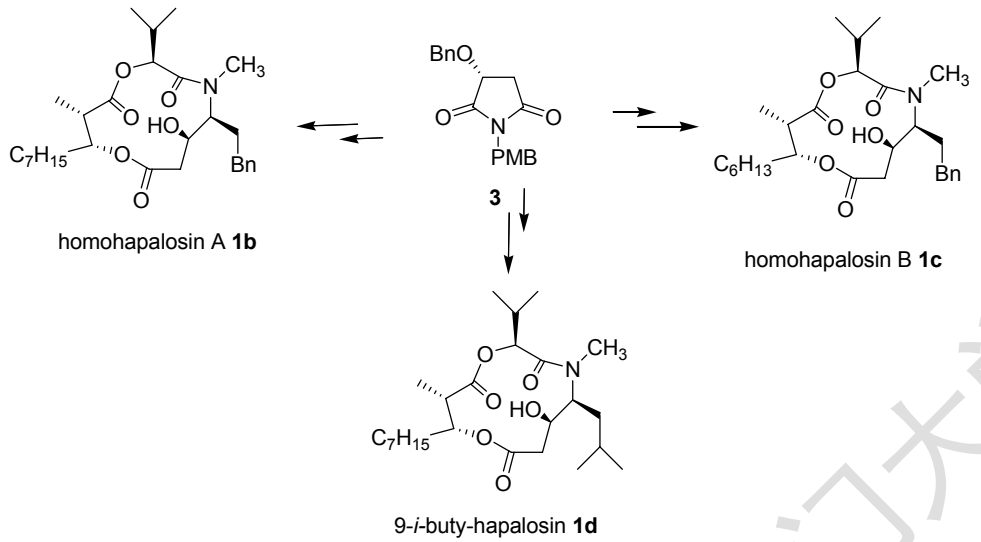


5. Total synthesis of hapalosin was completed in 13 steps with an overall yield of 16.9% starting from (*R*)-malimide. Thus a diversity-oriented asymmetric synthesis of hapalosin was developed.

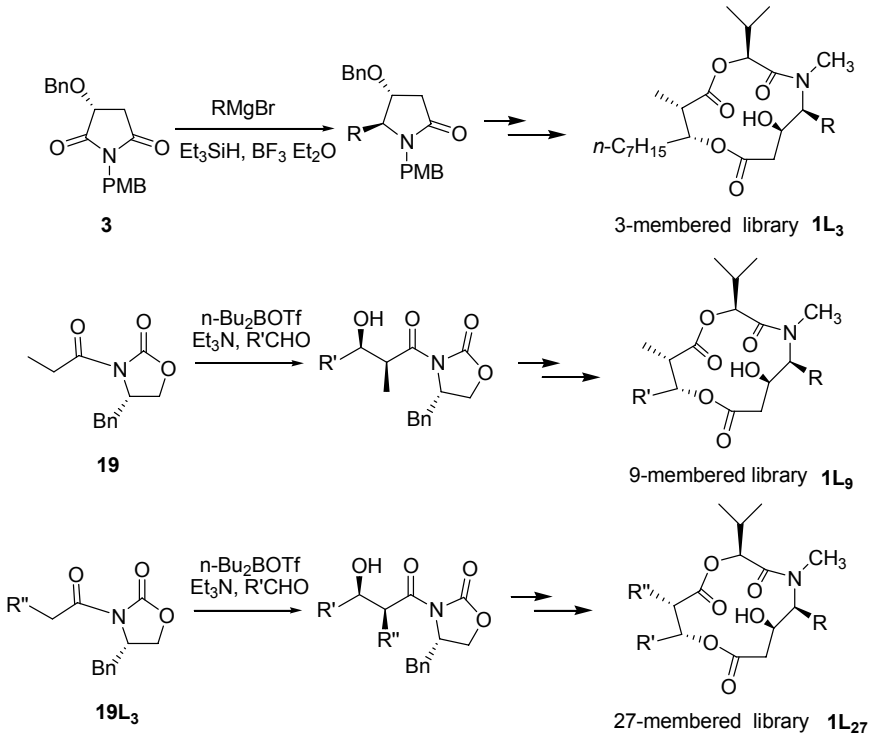




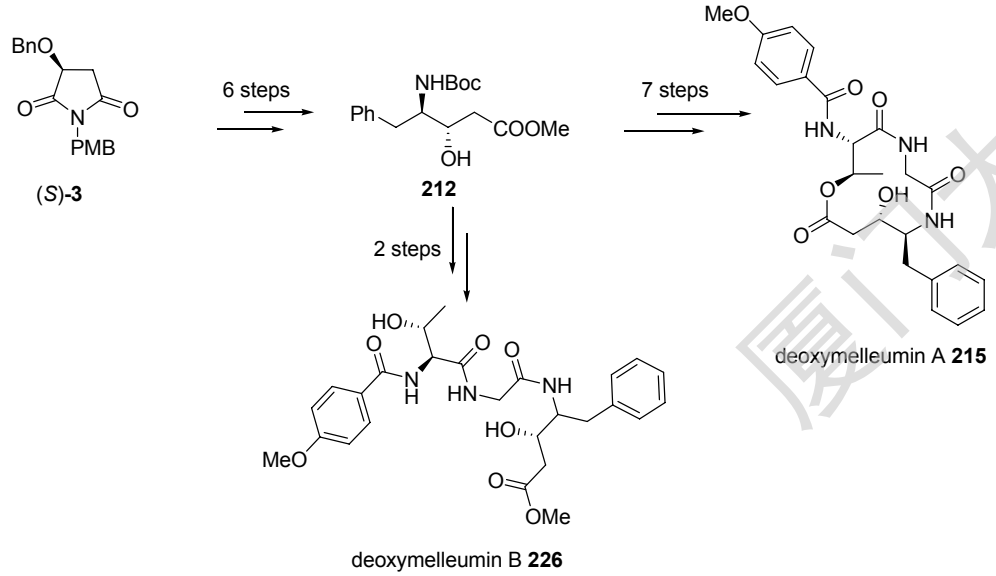
6. Diversified group was introduced to the *C*-5 of pyrrolidone through Grignard addition to the building block. Three hapalosin analogues modified at the *C*-9 (homohapalosin A, homohapalosin B and 9-*i*-butylhapaosin) were synthesized, based on the diversity-oriented asymmetric synthetic route.



7. The reductive alkylation of malimide using a library of three membered Grignard reagents allowes to construct a three-membered library of hapalosin analogues in 13 steps. Further more, the method of liquid combinational chemistry was introduced to the Evans aldol reaction, and two hapalosin analogues libraries contained 9 members and 27 members have been constructed in 9 steps respectively. It showed high yield and homogeneous in each synthetic step.



8. The non-natural amino acid **212** was synthesized from (*S*)-**3** in 6 steps. The asymmetric synthesis of deoxymelleumin A and deoxymelleumin B, the deoxy-analogues of the corresponding natural products melleumin A and melleumin B were achieved from **212** in 7 steps and 2 steps respectively. The accomplished work laid a basis for the total synthesis of the natural products melleumins A and B.



Key words: cylcopeptides; asymmetric synthesis; natural product; combinational chemistry; analogues; mutidrug resistance; hapalosin; melleumins.

缩略语简表

Ac	acetyl / 乙酰基
AIBN	azodiisobutyronitrile / 偶氮二异丁腈
Ar	aryl / 芳基
BBN (9-BBN)	9-borabicyclo[3.3.1]nonane / 9-硼杂双环[3.3.1]壬烷
Bn	benzyl / 苄基
Boc	*t*-butoxycarbonyl / 叔丁氧羰基
BOP-Cl	bis(2-oxo-3-oxazolidinyl)phosphininic chloride
Bu_2BOTf	dibutylboron triflate / 三氟甲磺酸二丁基硼酯
Bz	benzoyl / 苯甲酰基
CAL-B	Candida Antarctica, fraction B / 南极洲假丝酵母
CAN	cericammomium nitrate / 硝酸铈铵
Cbz (Z)	benzyloxycarbonyl / 苄氧羰基
CDI	Carbonyl diimidazole / 羰基二咪唑
m-CPBA	*m*-chloroperoxylbenzoic acid / 间氯过氧苯甲酸
CSA	camphorsufonic acid / 樟脑磺酸
DBN	1,5-diazabicyclo[4.3.0]undec-5-ene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*'-dicyclohexylcarbodiimide / 二环己基碳二亚胺
DCU	*N*,*N*'-dicyclohexylurea / 二环己基脲
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate / 偶氮二甲酸二乙酯
DET	diethyl tartrate / 酒石酸二乙酯
DHP	3,4-dihydro-2H-pyran / 二氢吡喃
$(DHQ)_2PHAL$	bis(dihydroquinino)phthalazine
DIBAL (DIBAH)	diisobutylaluminum hydride / 二异丁基铝氢
DIPEA (Hünig's base)	diisopropylethylamine / 二异丙基乙基氨
DMAP	4-*N*,*N*-dimethylaminopyridine / 4-*N*,*N*-二甲氨基吡啶
DMF	*N*,*N*-dimethylformamide / *N*,*N*-二甲基甲酰胺
DMSO	dimethylsulfoxide / 二甲基亚砜
DPPA	diphenylphosphoryl azide / 二苯基磷酰基叠氮
EDC	1-ethyl-3-(3-dimethyllaminopropyl)carbodiimide / 1-乙基-3-(3-二甲胺丙基)碳二亚胺
EDCI	1-ethyl-3-(3-dimethyllaminopropyl)carbodiimide hydrochloride
Fmoc	9-fluroenylmethoxycarbonyl
HMDS	hexmethyldisilazane / 六甲基二硅基氨烷
HOAt	1-hydroxy-7-azabenzotriazole / 1-羟基-7-氮杂苯并三氮唑
HOBt	1-hydroxybenzotriazole / 1-羟基苯并三氮唑
HOSu	N-hydroxysuccinimide / N-羟基琥珀酰亚胺
Imid	imidazole / 咪唑

Ipc	isopinocamphenyl / 异松蒎基
LAH	lithium aluminum hydride / 氢化锂铝
LDA	lithium isopropylamide / 二异丙基氨基锂
lut	2,6-lutidine / 2, 6-二甲基吡啶
MDR	mutidrug resistance / 多药耐药
MOM	methoxylmethyl / 甲氧基甲基
NBS	*N*-bromosuccinimide / N-溴代琥珀酰亚胺
NCS	*N*-chlorosuccinimide / N-氯代琥珀酰亚胺
NMM	*N*-methylmorpholine / N-甲基吗啉
NMO	*N*-methylmorpholine oxide / N-甲基吗啉氧化物
NMP	*N*-methyl-2-pyrrolidinone / N-甲基吡咯烷酮
OBOP	one bead one peptide / 一株一肽
PCC	pyridinum chlorochromate / 氯铬酸吡啶盐
PDC	pyridinum dichromate / 重铬酸吡啶盐
PEG	polyethylene glycol / 聚乙二醇
Ph	phenyl / 苯基
PMB (MPM)	*p*-methoxybenzyl / 对甲氧基苄基
PMBTCAI	*p*-methoxybenzyl 2,2,2-trichloroacetimidate
PMP	*p*-methoxyphenyl / 对甲氧基苯基
PPTS	pyridinum *p*-toluenesulfonic acid / 对甲苯磺酸吡啶盐
PTSA(*p*-TsOH)	*p*-toluenesulfonic acid / 对甲苯磺酸
Py (pyr)	pyridine / 吡啶
TBAB	tetrabutylammonium bromide / 四丁基溴化铵
TBAF	tetrabutylammonium fluoride / 四丁基氟化铵
TBDPS	*t*-butyldiphenylsilyl / 叔丁基二苯基硅基
TBS (TBDMS)	*t*-butyldimethylsilyl / 叔丁基二甲基硅基
TBSOTf	*t*-butyldimethylsilyl triflate
TEA	triethylamine / 三乙胺
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy free radical
TFA	trifluoroacetic acid / 三氟乙酸
TfOH	trifluoromethanesulfonyl acid / 三氟甲磺酸
THF	tetrahydrofuran / 四氢呋喃
THP	2-tetrahydropyranyl / 四氢吡喃
TMEDA	*N*,*N*,*N*',*N*'-tetramethylethylene diamine / *N*,*N*,*N*',*N*'-四甲基乙二胺
TMS	trimethylsilyl / 三甲基硅基
Ts	p-toluenesulfonyl or Tosyl / 对甲苯磺酰基